



Applicants : T. DUBUFFET
J-P LECOUVE

JUN 07 2007

Serial No: 10/582,283

Filed : June 9, 2006

Title : Process for the synthesis of perindopril and its pharmaceutically acceptable salts.

Art Unit : 1626

Examiner : BARKER

Honorable Commissioner of Patents and Trademarks
Alexandria, V.A. 22313-1450

DECLARATION UNDER 37 CFR 1.132

I, Thierry DUBUFFET, a citizen of France, of 17, allée des Charmilles, 76190 AUTRETOT, France, declare and say that :

I hold the degree of Doctor of University of Paris, Faculty of Science, in 12/18/1989.

Between October 1990 and 09/30/2001, I have been Scientific Studies Manager at the Institut de Recherches Servier, France.

Since 10/01/2001, I have been Project Manager, in the Industrial Research Department of the plant at Oril Industrie, France.

I am the author or co-author of more than 25 international publications such as patents, scientific publications and communications.

I am one of the co-inventors of US Patent Application Serial n° 10/582,283 filed June 9, 2006, concerning a " Process for the synthesis of perindopril and its pharmaceutically acceptable salts ".

I am thoroughly familiar with the above-mentioned patent application and fully support the experiments contained therein which were performed either by me or under my supervision. I also fully support the conclusions derived therefrom and the arguments presented as concerns the inventive step of process described.

US 4,914,214 discloses the coupling reaction between (2S,3aS,7aS)-octahydroindole-2-carboxylic acid benzyl ester and N-[(S)-1-carboxybutyl]- (S)-alanine ethyl ester, using dicyclohexylcarbodiimide (DCC) / 1-hydroxybenzotriazole (HOBT) as a coupling agent, in the presence of triethylamine as a base.

A comparative study has been done, using :

- 1) in a first experiment : 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDCI) / 1-hydroxybenzotriazole (HOBT) as a coupling agent, in the presence of triethylamine as a base,
- 2) in a second experiment : propanephosphonic anhydride (T₃P) as a coupling agent, in the presence of triethylamine as a base.

The results are summarized in the following Table :

Experiment	Coupling agent	Base	Yield	Purity (isolated benzyl ester)
1	EDCI / HOBT 0.5 equivalent	triethylamine (1 equivalent)	91.0%	98.1%
2	T ₃ P	triethylamine (5 equivalents)	95.9%	98.1%
3 (reference)	DCC / HOBT 0.5 equivalent	triethylamine (1 equivalent)	91.9%	89%

All the experiments have been performed in acetonitrile (4 ml/g).

The chemical purity has been determined by HPLC.